nature reviews endocrinology

https://doi.org/10.1038/s41574-024-01025-4

Review article

Check for updates

Thyroid nodules: diagnosis and management

Giorgio Grani, Marialuisa Sponziello, Sebastiano Filetti & Cosimo Durante

Abstract

Thyroid nodules, with a prevalence of almost 25% in the general population, are a common occurrence. Their prevalence varies considerably depending on demographics such as age and sex as well as the presence of risk factors. This article provides a comprehensive overview of the prevalence, risk stratification and current management strategies for thyroid nodules, with a particular focus on changes in diagnostic and therapeutic protocols that have occurred over the past 10 years. Several sonography-based stratification systems (such as Thyroid Imaging Reporting and Data Systems (TIRADS)) might help to predict the malignancy risk of nodules, potentially eliminating the need for biopsy in many instances. However, large or suspicious nodules necessitate cytological evaluation following fine-needle aspiration biopsy for accurate classification. In the case of cytology yielding indeterminate results, additional tools, such as molecular testing, can assist in guiding the management plan. Surgery is no longer the only treatment for symptomatic or malignant nodules: active surveillance or local ablative treatments might be beneficial for appropriately selected patients. To enhance clinician–patient interactions and discussions about diagnostic options, shared decision-making tools have been developed. A personalized, risk-based protocol promotes high-quality care while minimizing costs and unnecessary testing.

Sections

Introduction

Epidemiology and diagnosis of thyroid nodules and thyroid cancer

Long-term management and treatment

Conclusions

Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy. e-mail: cosimo.durante@uniroma1.it

SHOUT
SHARE
IT

Key points

- Thyroid nodules are a common occurrence, with a prevalence of ~25% in the general population that varies widely according to age, sex and risk factors.
- The US Preventive Services Task Force recommends against screening for thyroid cancer in the general, asymptomatic adult population, as such screening would result in harms that outweigh potential benefits.
- If a thyroid nodule is suspected, the first step is to perform dedicated ultrasonography; ultrasonography risk stratification systems can classify and estimate the likelihood of malignancy of a nodule.
- If the need for further assessment is confirmed, a fine-needle aspiration biopsy is often performed; cytology results are usually classified according to a standard cytology reporting system.
- At the end of the initial diagnosis and risk stratification procedure, over 90% of nodules are found to be benign and asymptomatic; the patients are euthyroid and require no specific treatment.
- Preservation of thyroid function is of paramount importance; several non-surgical and minimally invasive techniques are available but, if surgery is needed, the minimal possible extent should be chosen.

Introduction

A thyroid nodule is a discrete lesion within the thyroid gland that can be distinguished from the surrounding thyroid tissue using sensitive imaging techniques. The use of these imaging techniques has led to an increase in the detection of thyroid nodules whose existence would otherwise have been unknown as well as to concerns about the unnecessary diagnosis of subclinical thyroid diseases[1,2]. The majority of thyroid nodules (up to 90%) are usually non-cancerous[3,4] (including thyroid follicular nodular disease (previously known as multinodular goitre), follicular adenomas and oncocytic adenomas), therefore, the primary goal of clinical investigations is to exclude malignancy (which, from a histological point of view, might include papillary, follicular, oncocytic, medullary and anaplastic thyroid cancers). The diagnostic process for thyroid nodules should strike a balance between determining their clinical significance and unnecessary overdiagnosis and, consequently, overtreatment.

The incidence of thyroid cancer has been consistently reported to be increasing in most high-income countries, primarily due to the increased detection of low-risk subclinical papillary thyroid carcinoma (PTC)[5,6]. Up to 53.6% of thyroid cancers are small and confined within the thyroid gland[7]. These cancers have an indolent nature and can be safely managed conservatively[8]. A wise and conservative approach to thyroid nodules can help identify the few cases that require immediate or extensive treatment while minimizing, for most patients, issues associated with treatment such as hypothyroidism, surgical complications and financial burden. Amongst all cancer types, thyroid cancer in particular causes a high degree of financial burden to patients, and survivors of thyroid cancer report higher rates of bankruptcy compared with survivors of other cancer types[3,9].

Based on these premises, it is becoming increasingly necessary to provide an overview of the diagnostic and therapeutic protocols for individuals with thyroid nodules. Patient age, medical history and life expectancy, as well as the risk of neoplasm-related symptoms, should be considered when making decisions. This Review aims to outline changes in diagnostic and therapeutic protocols over the past 10 years. Specifically, it discusses the laboratory and radiography work-ups for all nodules as well as the different management strategies for symptomatic, functioning and/or malignant thyroid nodules.

Epidemiology and diagnosis of thyroid nodules and thyroid cancer

The prevalence of thyroid nodules increases with age, is higher in female individuals and varies by country as well as by the detection method (palpation, ultrasonography or autopsy)[10,11]. A 2022 systematic review and meta-analysis reported an overall prevalence of nodules in the general population of 24.8% (95% CI 21.4–28.6)[11]. As well as sex and age[12], factors such as iodine deficiency[13] and metabolic syndrome[14,15], in addition to individual components of metabolic syndrome, such as hypertension[16,17], body mass index[18], adiposity[19] and metabolic dysfunction-associated steatotic liver disease (also known as non-alcoholic fatty liver disease)[11], have been reported to be positively associated with the prevalence of thyroid nodules. A considerable proportion of nodules are asymptomatic, even in selected patients referred for surgery. A multicentre analysis[20] conducted in 2022 investigating the detection methods of thyroid nodules in a cohort of 1,328 patients undergoing thyroid surgery reported that 448 (34%) discovered thyroid nodules as a result of thyroid-related symptoms, 184 (14%) showed symptoms of other endocrine conditions, while 542 (41%) were completely asymptomatic. The detection mode of the remaining 154 nodules (12%) was unknown. Thyroid carcinoma was diagnosed in 613 individuals (46% of the total), of whom 310 (51%) did not present any thyroid-related symptoms. The median size of the cancers in the symptomatic group was 2.6 cm (range 0.2–10.5), whereas it was 1.7 cm (range 0.05–8.80) in the asymptomatic patients[20].

Incidental thyroid nodules are commonly detected as a result of the widespread use of imaging techniques such as ultrasonography, CT, MRI and PET–CT to assess other tissues or organs located nearby (for example, the carotid arteries, parathyroid glands, cervical lymph nodes, internal jugular veins and other structures in or outside the neck)[21]. Fluorodeoxyglucose-avid thyroid nodules are frequently (1–4%) found during staging of other cancers. The risk of malignancy in an incidentally discovered fluorodeoxyglucose-avid nodule is unclear due to selection biases but is likely to be less than 15%[22].

Regardless of the means by which incidental thyroid nodules are discovered, it is important to consider the entire clinical picture to determine the most appropriate course of action. If the patient has a life expectancy of less than 5 years, further investigation is unlikely to be beneficial[22]. As exceptions, if the lesion is larger than 4 cm, is suspected to be a metastasis, or the source of metastases in the case of patients with metastasis and unknown primary malignancy, further diagnostic work-up is always needed[22]. For patients with a life expectancy of more than 5 years, all nodules should undergo dedicated thyroid ultrasonography for further risk stratification[21,22]. All subsequent decisions depend on the ultrasonography findings.

Ultrasonography

Ultrasonography screening programmes. The US Preventive Services Task Force (USPSTF) has, since 2017, recommended against screening for thyroid cancer in the general, asymptomatic adult population due to any benefits being outweighed by potential risks (for example, biopsy

risks (haematoma, needle tract seeding) and surgery risks (hypothyroidism, hypoparathyroidism, recurrent laryngeal nerve palsy))[23,24] (Fig. 1). This recommendation has been challenged by some clinicians[25]. For example, a systematic review and meta-analysis of 12 studies showed that thyroid cancers incidentally detected through imaging methods were smaller and had lower rates of aggressive histology, lymph node

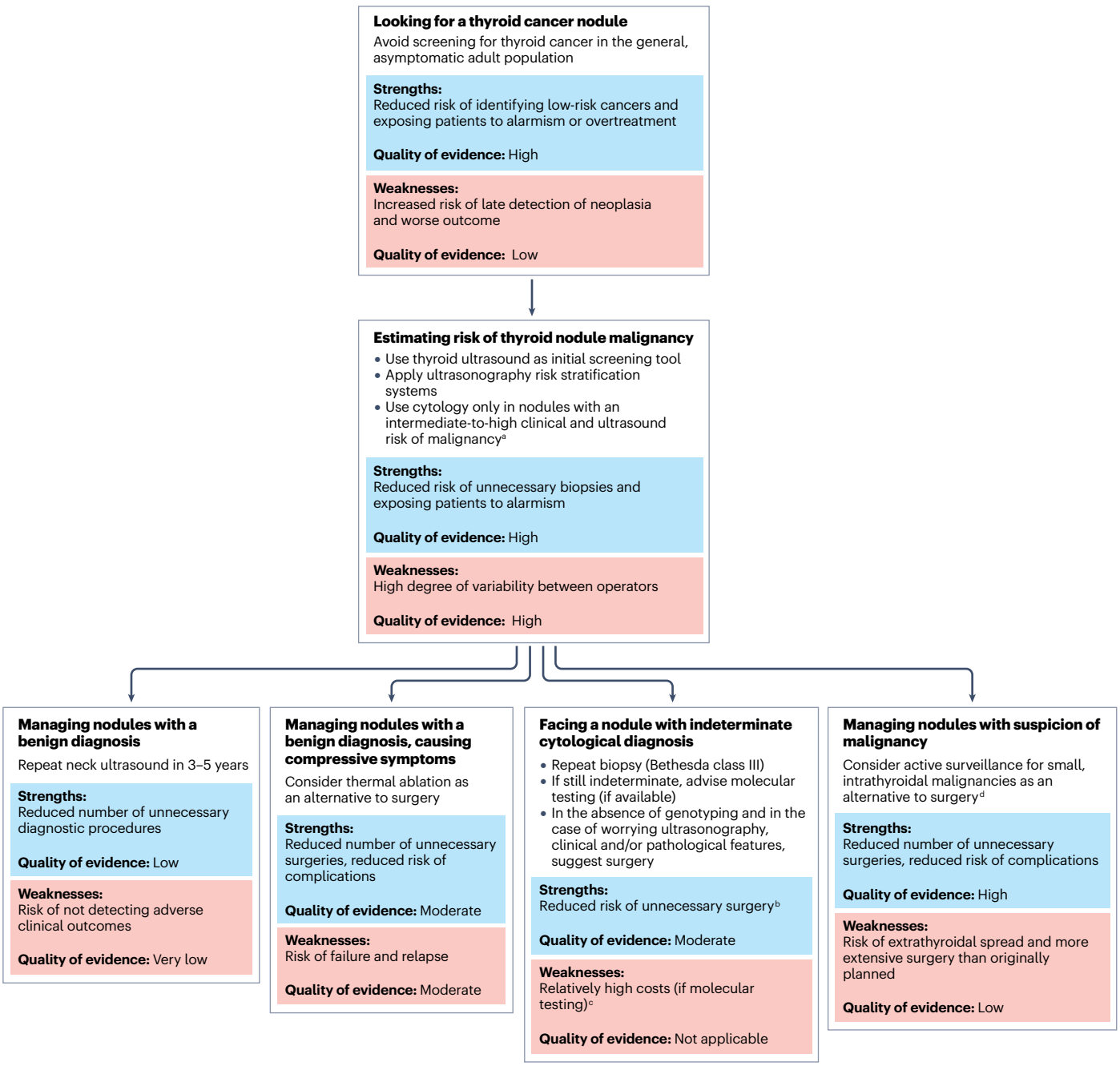
Looking for a thyroid cancer nodule
Avoid screening for thyroid cancer in the general, asymptomatic adult population
Strengths:
Reduced risk of identifying low-risk cancers and exposing patients to alarmism or overtreatment
Quality of evidence: High
Weaknesses:
Increased risk of late detection of neoplasia and worse outcome
Quality of evidence: Low
Estimating risk of thyroid nodule malignancy
• Use thyroid ultrasound as initial screening tool
• Apply ultrasonography risk stratification systems
• Use cytology only in nodules with an intermediate-to-high clinical and ultrasound risk of malignancy[a]
Strengths:
Reduced risk of unnecessary biopsies and exposing patients to alarmism
Quality of evidence: High
Weaknesses:
High degree of variability between operators
Quality of evidence: High
Managing nodules with a benign diagnosis
Repeat neck ultrasound in 3–5 years
Strengths:
Reduced number of unnecessary diagnostic procedures
Quality of evidence: Low
Weaknesses:
Risk of not detecting adverse clinical outcomes
Quality of evidence: Very low
Managing nodules with a benign diagnosis, causing compressive symptoms
Consider thermal ablation as an alternative to surgery
Strengths:
Reduced number of unnecessary surgeries, reduced risk of complications
Quality of evidence: Moderate
Weaknesses:
Risk of failure and relapse
Quality of evidence: Moderate
Facing a nodule with indeterminate cytological diagnosis
• Repeat biopsy (Bethesda class III)
• If still indeterminate, advise molecular testing (if available)
• In the absence of genotyping and in the case of worrying ultrasonography, clinical and/or pathological features, suggest surgery
Strengths:
Reduced risk of unnecessary surgery[b]
Quality of evidence: Moderate
Weaknesses:
Relatively high costs (if molecular testing)[c]
Quality of evidence: Not applicable
Managing nodules with suspicion of malignancy
Consider active surveillance for small, intrathyroidal malignancies as an alternative to surgery[d]
Strengths:
Reduced number of unnecessary surgeries, reduced risk of complications
Quality of evidence: High
Weaknesses:
Risk of extrathyroidal spread and more extensive surgery than originally planned
Quality of evidence: Low

Fig. 1 | Guide to best practices regarding the diagnosis and management of thyroid nodules. The figure outlines the main stages that a clinician managing thyroid nodules must navigate, starting from the detection of the thyroid nodule to making treatment decisions. The quality of evidence is derived from the references included and discussed in the corresponding sections of the text. Quality of evidence was rated as high (further research is very unlikely to change our confidence in the estimate of effect), moderate (further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate), low (further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate), or very low (we are very uncertain about the estimate), according to GRADE guidelines[24]. [a]Low-risk nodules that have been enlarged to the extent that they exert a mass effect and that are eligible for treatment might be suitable for cytological examination. [b]Long-term follow-up studies of patients who have not undergone surgery are still lacking. [c]Cost-effectiveness of molecular testing is still a debated issue and varies in different regions[93–95]. [d]Refers to nodules with indeterminate cytology (Bethesda class III and IV) with a suspicious sonography pattern or positive molecular test; and nodules with Bethesda class V and VI cytology.

Box 1 | Wilson and Jungner principles of screening published by the WHO[28]

1. The condition should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic phase.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including a diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuous process and not a 'once and for all' project.

Box 1 reprinted with permission from ref. 28, the World Health Organization.

metastasis and distant metastasis than non-incidental thyroid cancer (detected due to clinical signs or symptoms). These differences in pathological characteristics resulted in about a 60% lower recurrence rate and a 70% lower thyroid cancer-specific mortality rate in patients with incidental thyroid cancers than in patients with non-incidental thyroid cancers[26]. However, these types of study are susceptible to lead-time bias (the time between the detection of a disease by screening and its usual clinical presentation): the earlier time of diagnosis can make screening appear to increase survival, even if there is no change in the usual course of the disease. In addition, so-called length-time bias could enrich screening-detected neoplasms with indolent ones and thereby confer an apparent improvement in survival[27].

The USPSTF recommendation does not apply to individuals who are at increased risk of thyroid cancer due to a history of exposure to ionizing radiation (in childhood, as radioactive fallout; during medical treatment, as low-dose radiotherapy for benign conditions or high-dose radiation for malignancy), inherited genetic syndromes associated with thyroid cancer (for example, familial adenomatous polyposis), or having one or more first-degree relatives with a history of thyroid cancer. However, even in these cases, current evidence does not support an ultrasonography-based screening programme because the evidence of benefit does not fulfil all the WHO criteria for an appropriate screening programme[28,29] (Box 1). Neck palpation in these individuals can provide a practical compromise between the high sensitivity of ultrasonography and the limitations of no screening at all. However, it is important to note that a thyroid cancer found in a palpable nodule is likely to be clinically significant, suggesting a high-risk neoplasia.

Ultrasound screening of apparently healthy relatives of individuals with an established diagnosis of differentiated thyroid cancer is likely to detect a high prevalence of nodules and a low prevalence of cancer[27] and is associated with high costs[28]. However, a higher prevalence of cancer was detected in kindreds with at least three family members affected by thyroid cancer than in kindreds with one or two cases prior to screening, suggesting that closer surveillance might be warranted in these cases[30,31].

Dedicated thyroid ultrasonography. When a thyroid nodule is suspected or detected, the first step is to perform a thyroid ultrasound scan (Fig. 1) using high-resolution linear probes to provide clear images of the gland. This examination is painless, safe and can be performed swiftly in various healthcare settings. To obtain an initial risk evaluation, the examiner should focus on certain key features. These features include nodule echogenicity, composition (solid, cystic or mixed), shape, margins and the presence of calcifications or other hyperechoic foci within the nodule; the characteristics of all cervical lymph nodes should also be noted. Nodule features such as solid composition, marked hypoechogenicity, irregular or infiltrative margins, punctate hyperechoic foci, extrathyroidal extension (extension of nodule tissue beyond the thyroid margin), and the presence of suspicious locoregional lymph nodes are consistently associated with malignancy[32]. However, the clinical significance of other features, such as taller-than-wide shape, mild hypoechogenicity or capsular abutment (where the nodule abuts the thyroid capsule), is also a matter of discussion[33]. Figure 2 depicts a number of ultrasonography features that might be indicative of thyroid nodule malignancy accompanied by guidance on how to recognize and describe them.

No single feature reliably differentiates malignant lesions from benign ones. Moreover, interpretation of these features often exhibits substantial interobserver variability[34]. As a result, multiple risk stratification systems (RSSs) that use certain ultrasonography features to classify nodules and estimate their likelihood of malignancy, thereby providing a predicted malignancy risk within a certain range (both qualitative and quantitative), have been developed. Most of these RSSs incorporate graduated nodule size cut-off limits to recommend either a fine-needle aspiration (FNA) biopsy or simple observation, with the general aim of reducing unnecessary biopsies. The ability of these RSSs to reduce the number of unnecessary cytological evaluations varies widely[35]. A 2023 network meta-analysis[36] compared six RSSs: the American Association of Clinical Endocrinologists, American College of Endocrinology and Associazione Medici Endocrinologi system[37]; the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TIRADS)[38]; the American Thyroid Association RSS[39]; the European Thyroid Imaging Reporting and Data System (EU-TIRADS), endorsed by the European Thyroid Association[40]; the Korean Thyroid Imaging Reporting and Data System (K-TIRADS), endorsed by the Korean Thyroid Association and the Korean Society of Thyroid Radiology[41]; and Kwak-TIRADS[42]. ACR TIRADS had the highest diagnostic performance for the exclusion of thyroid cancer by ultrasonography[36]. It is noteworthy that two of these systems (EU-TIRADS and K-TIRADS) have since had upgrades from the versions that were part of the meta-analysis[2,43,44]. Additionally, other widely used classification systems, such as the Chinese Thyroid Imaging Reporting and Data System, were not covered in the study[45]. Five of these systems[46] are summarized in Box 2. All five use an algorithmic approach to identify groups of sonography features that are associated with specific risks of malignancy. ACR TIRADS is different because it individually assesses and rates five main ultrasonography features of the nodule according to a numerical score: the sum of the five scores determines the risk class assigned to the nodule.

The presence of many different RSSs can be confusing and is slowing their real-life application[47]. There is some degree of heterogeneity across RSSs in terms of the definitions of nodule features, the relative weight assigned to them and the size thresholds used for FNA biopsy recommendations. The performance of each system in clinical practice might also vary according to specific feature definitions. For example, taller-than-wide shape (or non-parallel orientation) has

different definitions and is prone to overestimation when assessed subjectively[32,48,49]; the degree of echogenicity is also difficult to standardize, and less experienced operators might face difficulties in distinguishing different kinds of hyperechogenic spots. Furthermore, some ultrasonography features are emerging as key risk-modifying factors but are not currently included in RSSs (for example, the location of the nodule inside the gland[50–52]). In addition, patient-related characteristics, such as age, have been proposed as potential modulators of the ultrasound risk of malignancy[53–56].

To address these issues, an international multidisciplinary group of experts (the International Thyroid Nodule Ultrasound Working Group) was convened in 2018 with the goal of developing an international, unified system, tentatively called the International Thyroid Imaging Reporting and Data System (I-TIRADS). The group has two aims: to propose a lexicon and atlas of ultrasonography descriptors of thyroid nodules and to develop a new RSS to calculate the malignancy risk. The outcomes of the initial stage of the project, which entailed creating a common vocabulary for thyroid nodule ultrasound, were published in 2023 (ref. 57).

Artificial intelligence for the initial evaluation of thyroid nodules. Artificial intelligence encompasses several computer science approaches, including machine learning, whereby computers learn from data given by humans, and deep learning, which uses neural networks that copy brain function to analyse data. Several artificial intelligence systems have been developed for analysing and stratifying the risk of malignancy using ultrasonography images of thyroid nodules, with four platforms already approved by the FDA[58].

Two meta-analyses have explored current evidence for the use of artificial intelligence in the evaluation of thyroid nodules. One meta-analysis of 25 studies with 17,429 ultrasonography images of thyroid nodules showed that artificial intelligence-assisted tools had good diagnostic accuracy for the binary classification of thyroid nodules as benign or malignant, with a sensitivity of 88% (95% CI 0.85–0.90) and a specificity of 81% (95% CI 0.74–0.86)[59]. The other meta-analysis concluded that artificial intelligence had comparable performance to that of radiologists in this clinical context[60]. In some cases, artificial intelligence has been shown to exceed the performance of some less experienced physicians, and can potentially be used as a training tool and a decision support tool[61,62].

The use of artificial intelligence has also been explored in the evaluation of neck lymph nodes and cytopathology specimens. However, the clinical adoption of artificial intelligence in the evaluation of thyroid disease will require developers to demonstrate that their software is effective, usable in real-world settings and cost-effective[58].

Laboratory testing

Measurement of TSH. During the initial assessment of all patients with a thyroid nodule, it is recommended that serum levels of thyroid-stimulating hormone (TSH) be measured to determine whether or not the nodule is hyperfunctioning (a nodule that grows and produces

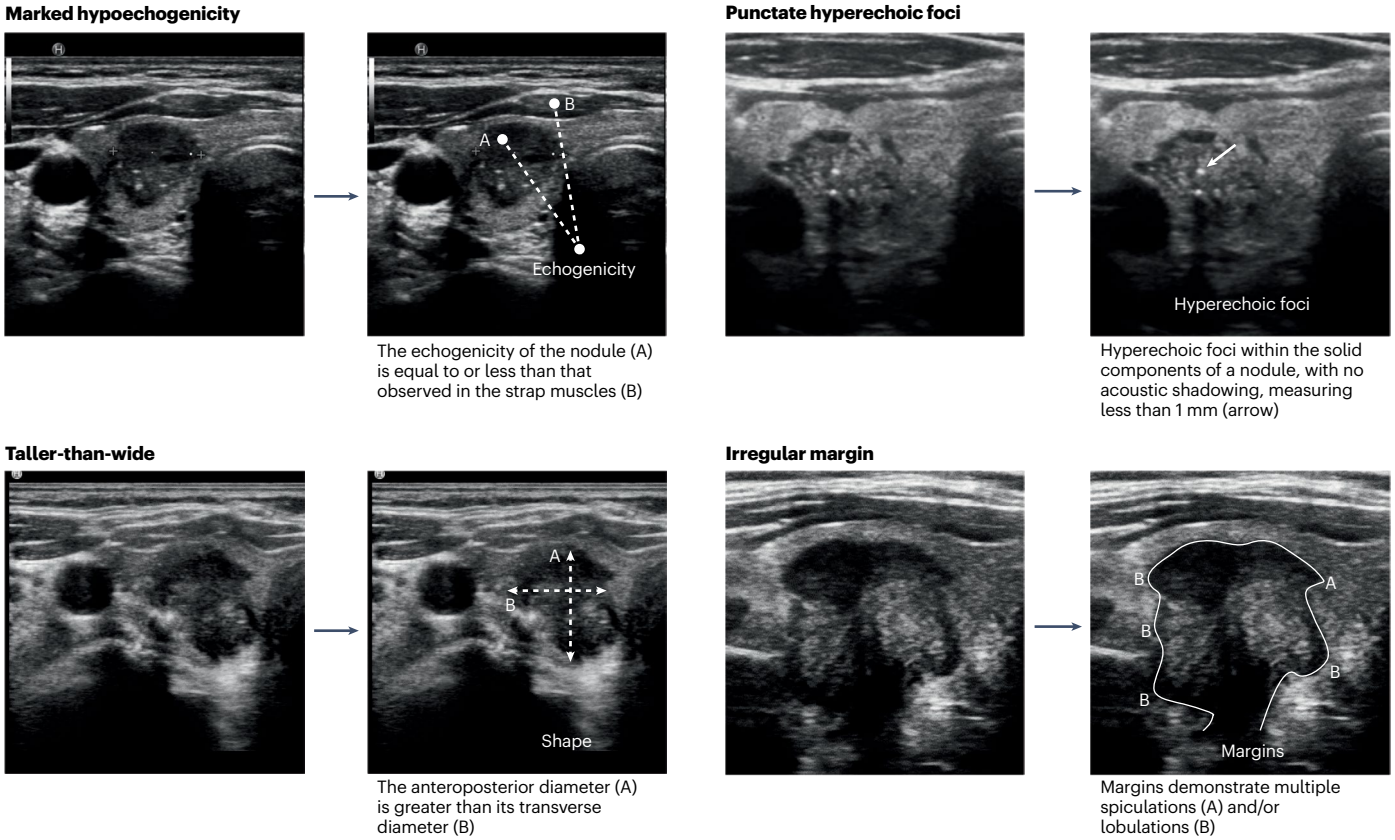

Fig. 2 | Cardinal sonographic features of malignant nodules with guidance for recognition and description. For each pair of images, the images in the left-hand panels represent the original ultrasonography images while those on the right are annotated copies revealing the suspicious features. The marked hypoechogenicity image pair is reprinted with permission from ref. 33, Wiley Publishing.

Box 2 | Overview of the standardized thyroid nodule ultrasound-based scoring systems proposed or endorsed by international practice guidelines[a]

AACE–AME–ACE[37]

Suspicious ultrasonography features

- Marked hypoechogenicity
- Spiculated or lobulated margins
- Microcalcifications
- Taller-than-wide shape
- Extrathyroidal growth
- Pathological adenopathy

Low risk (ROM 1%; FNA >20 mm (selective)[b])

- Cysts (fluid component >80%)
- Mostly cystic nodules with reverberating artefacts and not associated with suspicious ultrasonography signs
- Isoechoic spongiform nodules, either confluent or with regular halo

Intermediate risk (ROM 5–15%; FNA >20 mm)

- Slightly hypoechoic (versus thyroid tissue) or isoechoic nodules, with ovoid-to-round shape, smooth or ill-defined margins
- Intranodular vascularization, elevated stiffness at elastography, macro or continuous rim calcifications, or indeterminate hyperechoic spots might be present

High risk (ROM 50–90%[c]; FNA ≥10 mm (5 mm selective[d]))

Nodules with ≥1 of the following:

- Marked hypoechogenicity (versus prethyroid muscles)
- Spiculated or lobulated margins
- Microcalcifications
- Taller-than-wide shape (anteroposterior > transverse)
- Extrathyroidal growth
- Pathological adenopathy

ATA[39]

Suspicious ultrasonography features

- Irregular margins (infiltrative, microlobulated)
- Microcalcifications
- Taller-than-wide shape
- Rim calcifications with small extrusive soft-tissue component
- Evidence of extrathyroidal extension

Benign (ROM: <1%; FNA not indicated)

- Purely cystic nodules (no solid component)

Very low suspicion (ROM <3%; FNA ≥20 mm or observation)

- Spongiform or partially cystic nodules without any of the ultrasound features defining low-suspicion, intermediate-suspicion or high-suspicion patterns

Low suspicion (ROM: 5–10%; FNA ≥15 mm)

- Isoechoic or hyperechoic solid nodule, or partially cystic nodule with eccentric solid area without microcalcifications, irregular margin, extrathyroidal extension or taller-than-wide shape

Intermediate suspicion (ROM 10–20%; FNA ≥10 mm)

- Hypoechoic solid nodule with smooth margins without microcalcifications, extrathyroidal extension or taller-than-wide shape

High suspicion (ROM >70–90%; FNA ≥10 mm)

Solid hypoechoic nodule or solid hypoechoic component of partially cystic nodule with ≥1 of the following:

- Irregular margins (infiltrative, microlobulated)
- Microcalcifications
- Taller-than-wide shape
- Rim calcifications with small extrusive soft tissue
- Extrathyroidal extension

EU-TIRADS[36] (modified)[2]

Suspicious ultrasonography features

- Non-parallel orientation
- Irregular margins
- Microcalcifications
- Marked hypoechogenicity
- Extrathyroidal extension[e]

Benign (EU-TIRADS 2) (ROM 0%; FNA not indicated)

- Anechoic (purely cystic)
- Entirely spongiform nodules

Low risk (EU-TIRADS 3) (ROM 2–4%; FNA >20 mm)

- Oval shape, smooth margins, isoechoic or hyperechoic, without any feature of high risk

Intermediate risk (EU-TIRADS 4) (risk of malignancy 6–17%; FNA >15 mm)

- Oval shape, smooth margins, mildly hypoechoic, without any feature of high risk

High risk (EU-TIRADS 5) (ROM 26–87%; FNA >10 mm)

Nodules with ≥1 of the following:

- Non-oval shape
- Irregular margins
- Microcalcifications
- Marked hypoechogenicity

K-TIRADS[37] (modified)[39,40]

Suspicious ultrasonography features

- Punctate echogenic foci
- Non-parallel orientation
- Irregular margins

Benign (ROM <1–3%; FNA not indicated)

- Isohyperechoic spongiform
- Partially cystic nodule with comet-tail artefact
- Pure cyst

(continued from previous page)

Low suspicion (ROM 3–10%; FNA >20 mm)
- Partially cystic or isohyperechoic nodule without any of the three suspicious ultrasound features

Intermediate suspicion (ROM 15–40%; FNA ≥10–15 mm)
- Solid hypoechoic nodule without any suspicious ultrasound features, or partially cystic or isohyperechoic nodule with any of the suspicious features
- Entirely calcified nodules

High suspicion (ROM >60%; FNA ≥10 mm (>5 mm selective)[f])
Solid hypoechoic nodule with any of the following:
- Punctate echogenic foci
- Non-parallel orientation
- Irregular margin

C-TIRADS[45]
Suspicious ultrasonography features (each feature adds a single point):
- Vertical orientation
- Solid composition
- Marked hypoechogenicity
- Microcalcifications
- Ill-defined and/or irregular margins and/or extrathyroidal extension

C-TR2 (–1 point) (ROM 0%; FNA not indicated)
- No suspicious features, comet-tail artefacts

C-TR3 (0 points) (ROM <2%; FNA not indicated)

C-TR4a (1 point) (ROM 2–10%; FNA ≥15 mm or >10 mm[g])

C-TR4b (2 points) (ROM 10–50%; FNA >10 mm or >5 mm[g])

C-TR4c (3–4 points) (ROM 50–90%; FNA >10 mm or >5 mm[g])

C-TR5 (5 points) (ROM >90%; FNA >10 mm or >5 mm[g])

AACE, American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; AME, Associazione Medici Endocrinologi; ATA, American Thyroid Association; C-TIRADS, Chinese Thyroid Imaging Reporting and Data System; EU-TIRADS, European Thyroid Imaging Reporting and Data System; FNA, fine-needle aspiration; K-TIRADS, Korean Thyroid Imaging Reporting and Data System; ROM, risk of malignancy. [a]The American College of Radiology Thyroid Imaging Reporting and Data System is not included in the table because it uses a different approach to assessing malignancy risk compared to the ultrasonography scoring systems reported here. While the scoring systems here identify groups of sonography features with specific risks, the American College of Radiology Thyroid Imaging Reporting and Data System assesses ultrasonography features individually and assigns a numerical score based on their risk level. The total risk of the nodule is then calculated by summing the scores of each individual feature. [b]Growing nodule, high-risk history, before surgery or local therapies. [c]In accordance with the presence of one or more suspicious findings. [d]FNA is recommended for the following nodules: subcapsular or paratracheal lesions; suspicious lymph nodes or extrathyroid spread; positive personal or family history of thyroid cancer; history of head and neck irradiation; coexistent suspicious clinical findings (for example, dysphonia). [e]Ultrasonography features suggestive of extrathyroidal extension are not included in the main features of the EU-TIRADS; however, they should prompt FNA irrespective of EU-TIRADS score. [f]Biopsy is recommended for small (>5 mm) high-suspicion (K-TIRADS 5) nodules with high-risk features (near the trachea or posteromedial capsule along the course of the recurrent laryngeal nerve). Biopsy might be considered for small (>5 mm and ≤10 mm) K-TIRADS 5 nodules without high-risk features to decide the management plan in adults. [g]Multiple nodules, adjacent to trachea or recurrent lanryngeal nerve. Box 2 is adapted from ref. 46, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

thyroid hormones independently of TSH). Most expert panels agree that further tests (including measuring serum levels of free tetraiodothyronine plus levels of total or free triiodothyronine, followed by a radionuclide scan to assess the uptake of radioactive iodine) should be conducted only if the serum levels of TSH are subnormal[2,39]. Subnormal levels of TSH might be indicative of a tumour that is producing excess thyroid hormones. However, the relationship between thyroid autonomy and TSH levels is affected by the degree of iodine sufficiency and varies widely regionally[63]. Consequently, some groups advocate for the use of a radionuclide scan regardless of TSH levels[64] or consideration of the iodine supply of the specific geographical area (for example, when TSH <1.0–1.5 mUI/l in iodine deficiency areas)[37,63]. A 'hot' nodule is indicative of an area or areas of increased tracer uptake on a radionuclide scan. Hot thyroid nodules are almost always benign adenomas on histology, having a 96–99% negative predictive value for malignancy[65].

Tumour markers. With regard to tumour markers, the routine measurement of serum levels of thyroglobulin for nodule evaluation is not recommended as thyroglobulin is typically produced by both benign and malignant thyroid cells; therefore, its predictive performance in the preoperative setting, when the thyroid is still in place, is limited. However, thyroglobulin is used as the standard tumour marker following total thyroidectomy, with increasing levels potentially indicating recurrent or metastatic cancer.

Measurement of serum levels of calcitonin is the most reliable test for diagnosing medullary thyroid cancer (MTC)[66], which originates from the parafollicular cells (C cells) of the thyroid that produce calcitonin, and allows this rare type of cancer to be detected at an earlier stage, thereby improving outcome[67]. A basal calcitonin level of >100 pg/ml is very suspicious for a diagnosis of MTC, while values between 10 and 100 pg/ml are indeterminate[68]. This grey area is influenced by many factors, including the sex of the patient (males have higher normal values than females)[69]. However, there are some issues with the specificity of the test and the cost-effectiveness of universal calcitonin screening of all nodules and therefore not all experts agree with its routine use in the initial work-up of thyroid nodules[2]. It should be taken into account that ultrasonography features (and RSSs) are not reliable for the diagnosis of MTC and that cytological examination shows poor sensitivity (~50%) for detecting MTC[66]. In some cases, MTC is misdiagnosed as oncocytic carcinoma or follicular thyroid cancer[70];

Table 1 | An overview of the standardized thyroid cytology reporting systems

Reporting system	Category	Description	ROM (%) or expected ROM (%)[a]
The Bethesda System for the Reporting of Thyroid Cytology (2023)[71b]	I	Non-diagnostic	13 (5–20)
	II	Benign	4 (2–7)
	III	Atypia of undetermined significance	22 (13–30)
	IV	Follicular neoplasm	30 (23–34)
	V	Suspicious for malignancy	74 (67–83)
	VI	Malignant	97 (97–100)
British Royal College of Pathologists (2022)[76]	Thy1	Non-diagnostic	12 (5–22)
	Thy1c	Non-diagnostic cystic lesion	NA
	Thy2	Non-neoplastic	5 (3–9)
	Thy2c	Non-neoplastic cystic lesion	NA
	Thy3a	Atypical features present	25 (20–31)
	Thy3f	Suspicious of follicular neoplasm	31 (24–39)
	Thy4	Suspicious of malignancy	79 (70–87)
	Thy5	Malignant	98 (97–99)
Italian Consensus for the classification and Reporting of Thyroid Cytology (SIAPEC-IAP 2014)[73]	TIR1	Non-diagnostic	NA
	TIR1c	Non-diagnostic cystic lesion	NA
	TIR2	Non-malignant or benign	<3
	TIR3a	Low-risk indeterminate lesion	<10
	TIR3b	High-risk indeterminate lesion	15–30
	TIR4	Suspicious of malignancy	60–80
	TIR5	Malignant	>95
Japanese Association of Endocrine Surgery and The Japanese Society of Thyroid Pathology (2019)[74c]	NA	Unsatisfactory	5.6
	NA	Cyst fluid	0.2–2
	NA	Benign	1.2
	NA	Undetermined significance	13.1
	NA	Follicular neoplasm	11.4
	NA	Suspicious for malignancy	95.8–98.8%
	NA	Malignant	99.2–99.3%
Royal College of Pathologists of Australasia (2020)[75]	1	Non-diagnostic	NA
	2	Benign	NA
	3	Indeterminate or follicular lesion of undetermined significance	NA
	4	Suggestive of a follicular neoplasm	NA
	5	Suspicious of malignancy	NA
	6	Malignant	NA

NA, not available; ROM, risk of malignancy. [a]Expected ROM for Bethesda system and Italian consensus. [b]For adults, including non-invasive follicular neoplasm with papillary-like nuclear features. [c]Single centre experience, including resected and unresected nodules.

thus, if cytology yields indeterminate results, it might be useful to carry out a calcitonin test.

Cytology

Cytological assessment is carried out on FNA biopsy samples. Cytology results are typically classified according to a standard cytology reporting system, such as the Bethesda System for Reporting Thyroid Cytopathology (BSRTC), proposed by an expert panel at the US National Institutes of Health in Bethesda, Maryland. The first edition of the system was published in 2009, with updates in 2018 and 2023 (refs. 71,72). Samples are classified as benign when they comprise colloid and monolayered follicular cells that have nuclei with a uniformly granular chromatin pattern, for example; samples suspicious for malignancy can include nuclear syncytia or cells with pseudoinclusions. The BSRTC is widely used in the USA and provides a reliable diagnostic framework. Similar reporting systems have been proposed by scientific societies in other countries[73–76]. The expected rate of malignancy for each category in the different reporting systems is shown in Table 1. Each category is associated with a specific pattern of cytological features, and the risk of malignancy has been determined through retrospective or prospective validation studies[71,73–77]. The actual malignancy rates are influenced by the local (institutional) prevalence of malignancy, quality of the cytology sample and pathologist experience.

However, several potential diagnostic pitfalls might result in false-positive, false-negative, indeterminate or non-diagnostic results. In particular, cytology cannot reliably distinguish between follicular-patterned hyperplastic nodules, follicular adenomas, follicular carcinoma and some follicular subtypes of PTC. Consequently, in the BSRTC, these lesions are reported as indeterminate and assigned to Bethesda category III ('atypia of undetermined significance') or IV ('follicular neoplasm'). These findings are reported in ~15–25% of all thyroid cytologies and are associated with expected malignancy rates of 13–30% and 23–34%, respectively[71].

Several strategies exist for dealing with an indeterminate diagnosis. The traditional approach is to repeat the cytological assessment (for Bethesda category III cases and some exceptional category IV cases) prior to suggesting diagnostic surgery[78]. A repeat FNA can facilitate a definitive diagnosis of the nodule, classifying it as benign or malignant. However, if the nodule is confirmed to be cytologically indeterminate, the indiscriminate use of diagnostic surgery would result in a high number of avoidable interventions. Given the malignancy rate of less than 30%, approximately 70% of patients would undergo unnecessary surgery. Accordingly, a more modern approach to dealing with an indeterminate diagnosis involves molecular testing of cytology samples primarily to reduce the need for diagnostic surgery (see below[79,80]; Fig. 1). In addition, the most recent American and European statements and practice guidelines[2,71] endorse simple sonographic surveillance as a viable alternative approach to surgery based on the identified risk associated with certain sonographic patterns. Thyroid nodules classified with indeterminate cytology by the Bethesda system (categories III and IV) and with a low estimated risk of malignancy (below 5%) according to validated RSSs are likely to be benign on histological examination. The only potential risk associated with these nodules is volumetric growth. Therefore, inclusion in active surveillance programmes might be considered with the aims of identifying any potential malignancy that could have been missed on initial evaluation and monitoring growth[81]. Other options include the use of ancillary techniques, such as elastosonography[82,83] and contrast-enhanced ultrasonography[84], which aim to evaluate the tissue stiffness and microvascularity, respectively;

however, these and other techniques are difficult to standardize and are still undergoing development.

Molecular testing

Comprehensive molecular profiling of thyroid tumours has led to the development of ancillary molecular tests that can complement clinical, sonographic and cytological evaluations to stratify the risk of malignancy of cytologically indeterminate thyroid nodules. The primary aim in this setting is to reduce the need for diagnostic surgery. However, as discussed later, molecular examination of thyroid FNA samples can additionally be used to identify prognostic biomarkers (thus potentially guiding the extent of surgery) or predictive biomarkers in patients already diagnosed with thyroid cancer to assess the chances of a positive patient response to the therapy.

For diagnosis. Commercially available tests exist that analyse several molecular characteristics, including somatic mutations, gene expression levels and microRNA classifiers[79,80]. The two most commonly used tests are the ThyroSeq v3 Genomic Classifier and the Afirma Genomic Sequencing Classifier (GSC). The ThyroSeq v3 examines 112 thyroid cancer-related genes for mutations, gene fusions, copy number changes or abnormal gene expression using next-generation sequencing[85]. On the basis of the probability of cancer, the results are classified by a unique genomic classifier as positive (risk of malignancy (ROM) 30–100%), negative for all tested alterations (ROM 3%), or currently negative due to the presence of a low-risk or low-level alteration (ROM <10%). A clinical validation study carried out on indeterminate thyroid nodules demonstrated 94% sensitivity and a negative predictive value (NPV) of 97%. Consequently, the authors of the study concluded that up to 61% of patients could avoid diagnostic surgery[86].

The latest version of Afirma GSC employs an RNA sequencing approach and features 12 classifiers, including 10,196 genes. Based on the likelihood of cancer, the Afirma results are categorized as either benign (ROM 4%) or suspicious (ROM 50%). The new version has improved in correctly categorizing a greater number of indeterminate nodules as benign compared with its previous version (the Gene Expression Classifier), thereby decreasing the number of unnecessary surgeries[87]. The sensitivity of the test is 91.1% and its NPV is 96.1%[88]. Indeterminate thyroid nodules with an Afirma GSC-suspicious result or with cytologically suspicious or malignant nodules can further benefit from the Afirma Xpression Atlas to identify expressed variants and gene fusions across 593 genes[89]. An Afirma Xpression Atlas-positive result is associated with a high risk of malignancy in Afirma GSC-suspicious nodules. This result might inform personalized patient management. However, it is important to note that Afirma GSC nodules that are suspicious but have a negative Afirma Xpression Atlas result still pose a considerable risk of being malignant[90].

A randomized clinical trial comparing the diagnostic performances of ThyroSeq v3 and Afirma GSC found no statistically significant differences in sensitivity (97% versus 100%, respectively) or specificity (85% versus 80%, respectively)[91]. These testing assays allowed 49% of patients with indeterminate nodules to avoid diagnostic surgery. Currently, both ThyroSeq and Afirma assays have NPVs that make them suitable for rule-out testing. It should be noted that the performance of the tests in the clinical validation studies was evaluated in surgically resected nodules. Therefore, the real clinical impact of the obtained NPVs and the benign call rates (the percentage of cytologically indeterminate cases that later result in a 'benign' or 'negative' molecular diagnosis[92]) remain to be established through the long-term follow-up of patients with 'test-negative' nodules who have not undergone surgery.

When selecting a molecular test, factors other than diagnostic performance might be considered. These factors include costs, processing time, sample rate and the ability to provide further prognostic information that might help guide the optimal management strategy. The high cost of most, though not all, commercial molecular tests is a major barrier to equitable access. The cost-effectiveness of molecular testing is still a matter of debate[93,94]. When comparing diagnostic surgery with molecular testing for the management of indeterminate nodules, the two major molecular approaches were found to be more cost-effective than diagnostic lobectomy[93,94]. ThyroSeq v3 was also found to be more cost-effective than Afirma GSC[94]. However, most of these analyses were based on simulation modelling, and results can vary depending on the actual test performance parameters, malignancy rates, the hypothesized surgical procedure and estimated complication rates. All these variables can differ significantly among institutions and countries. In a specific public, single-payer system, molecular testing at the current list price is unlikely to be cost-effective compared with diagnostic lobectomy (for example, this conclusion was the result of a health technology assessment analysis performed in Ontario, Canada)[95].

Of note, an analysis conducted in 2024 reported that the increased use of molecular testing in the USA failed to affect thyroidectomy rates[96]. To overcome this outcome, molecular testing could be integrated into an interdisciplinary diagnostic pathway that includes clinical, morphological and ultrasonography data[97]. The few studies that have used this approach demonstrated that molecular testing performs better in ruling out malignancy in sonographically low or intermediate-suspicion thyroid nodules than in sonographically high-suspicion nodules, although these results are still under debate[98,99].

The appropriate selection of samples for molecular testing is crucial[95,100]. Repeat FNA cytology can guide the selection of cytologically indeterminate thyroid nodules that warrant molecular testing. Nodules assigned to atypia of undetermined significance or follicular neoplasm categories that are classified as benign on repeat FNA have a very low risk of cancer or non-invasive follicular neoplasm with papillary-like nuclear features and are unlikely to benefit from molecular testing[101]. Performing molecular testing only in nodules with confirmed indeterminate cytology would further reduce the rate of diagnostic surgery for histologically benign nodules, while missing only rare low-risk tumours[102].

For prognosis and treatment. The primary clinical objective of molecular testing for patients with Bethesda class III and IV thyroid nodules is to avoid diagnostic surgery. However, the molecular details gained from testing can also provide prognostic information for the management of Bethesda class III to VI nodules. A multicentre study conducted in 2023 has shown that the cytology class is linked to the molecular profile (*BRAF*-like or *RAS*-like, according to the Cancer Genome Atlas study classification)[103]. Specifically, nodules with *RAS*-like alterations are less aggressive and more commonly found among Bethesda III and IV category cases than are nodules with *BRAF*-like alterations, which are more likely to be found in Bethesda V and VI categories[103]. *RAS*-like alterations are still considered molecularly indeterminate for cancer, but data have shown that nodules with *RAS*-like mutations can be further risk stratified by additional molecular testing[104] or by adding ultrasonography, cytology and clinical assessment to the diagnostic pathway to avoid overtreatment of benign nodules[99]. For *BRAF*-like nodules, molecular testing might provide useful information before surgery to better determine the risk of the neoplasm and the extent

of surgical intervention required. In 6% of cases in the study, high-risk molecular alterations (for example, *TERT* promoter mutations, usually considered late events) were found during molecular testing, which could indicate an aggressive tumour[103]. These patients could potentially be offered timely treatment and extensive surgery. However, it remains unclear whether, and to what extent, these molecular profiles influence actual patient outcomes. Other factors such as nodule size and ultrasonography appearance should in all cases be considered in the treatment of patients at high risk.

Comprehensive molecular profiling can provide valuable information for future therapeutic choices such as the selection of a molecularly targeted drug in the case of more advanced cancer. For cancers with *BRAF* V600E, the BRAF plus MEK inhibitor combination strategy (dabrafenib + trametinib) can be employed. Selective inhibitors that target RET (selpercatinib or pralsetinib) can be utilized for the treatment of *RET*-altered thyroid cancers, while inhibitors of neurotrophic tyrosine receptor kinase (NTRK) (entrectinib or larotrectinib) can be used for cancers that have *NTRK* fusions[105].

Long-term management and treatment

Once a diagnostic work-up has been completed, thyroid nodules might require treatment or periodic re-assessment based on their sonographic and cytological classification, as outlined below.

Sonographically or cytologically benign nodules

More than 90% of nodules, following their initial detection, are found to be either sonographically or cytologically benign and asymptomatic; the patients are euthyroid and do not require any specific treatment. Long-term follow-up is typically advised to detect any malignancy missed at the initial evaluation and to exclude the development of compressive symptoms or 'toxic' nodules responsible for hyperthyroidism (by producing excess thyroid hormones)[106]. However, these events are overall rare. The residual risk of malignancy in a nodule initially classified as benign on FNA biopsy is ~4% (2–7%)[71], with rates as low as 1.1% being reported in a long-term cohort study[107]. Rapid nodule growth is observed in ~15% of patients with a sonographically or cytologically benign nodule[108,109]. Predictors of rapid nodule growth include the presence of multiple nodules, main nodule volumes >0.2 ml and male sex. It is possible to anticipate the future behaviour of nodules by considering the growth rate calculated over 3 years of follow-up since the initial evaluation[109]. The appearance of new nodules is reported in ~10% of patients but only 3–6% of these nodules require biopsy as recommended by the RSSs[110].

Each of these considerations supports a re-evaluation of current follow-up strategies and a reduction in follow-up frequency when dealing with sonographically or cytologically benign and asymptomatic nodules. However, evidence-based guidance is still lacking. A scoping review attempting to compare different ultrasonography follow-up intervals in patients with benign thyroid nodules found very little robust evidence to determine the best ultrasonography follow-up protocols for thyroid nodules with a low-risk sonographic pattern and/or a benign cytology[111]. Clinical guidelines, mostly based on expert opinion, suggest that such nodules larger than 1 cm should be reassessed after 3–5 years, with the possibility of reclassification. This re-assessment would allow re-evaluation of the surveillance interval or even discontinuation of further follow-up[2]. The frequency of assessments could subsequently be reduced if no changes are observed and the initial growth rate is slow (less than 0.2 mm/year). Other clinical features, such as age and comorbidities, should be taken into account. As the risk of malignancy[53,56] and volumetric growth[108] both decrease with age, discontinuation of long-term follow-up might be proposed in older age (for example, over 65 years).

In the absence of hypothyroidism, thyroid hormone treatment for the management of benign thyroid nodules is discouraged because of its lack of efficacy in nodule size reduction and due to the potential risks associated with such therapy (increased morbidity and mortality)[2].

Cytologically benign nodules causing symptoms

Changes in thyroid hormone secretion. If the levels of serum TSH are higher than the reference range, levels of free tetraiodothyronine and anti-thyroid peroxidase antibody should be assessed to quantify the degree of hypothyroidism and to explore the presence of autoimmune thyroiditis. If hypothyroidism is confirmed, thyroid hormone treatment is appropriate. Hot, 'toxic' nodules, which are responsible for hyperthyroidism, are eligible for radioiodine treatment[112]. This therapy achieves euthyroidism within 3–12 months in 75–95% of patients with a solitary toxic nodule or toxic multinodular goitre and reduces the volume of multinodular goitres by ~50–60% after 2–5 years. However, the individual response varies with thyroid volume and is difficult to predict. The treatment can be repeated if further goitre reduction is needed[112].

Compressive symptoms. When thyroid nodules grow, they can lead to neck discomfort, pressure symptoms and cosmetic concerns, all of which can adversely affect the quality of life. Surgery is the traditional treatment for these nodules but the preservation of thyroid function is of paramount importance. This goal can be achieved by using the least invasive surgical approach, such as lobectomy and isthmusectomy, rather than a total thyroidectomy. Alternatively, non-surgical and minimally invasive techniques can be employed (Fig. 1). These alternatives include percutaneous ethanol injection (for cystic lesions), thermal ablation (for example, laser ablation, radiofrequency ablation and microwave ablation)[4] and non-invasive, high-intensity focused ultrasound[113]. These techniques differ with respect to their indications, side effects and associated costs[4].

The primary role in treating these cytologically benign but compressive nodules is the avoidance of unnecessary surgeries and their associated complications (hypothyroidism, postoperative bleeding, voice change or recurrent laryngeal nerve paralysis). A meta-analysis conducted in 2023 found ultrasound-guided radiofrequency and microwave ablation to be more effective and safer than conventional surgery or watchful waiting for patients with benign thyroid nodules; these treatments resulted in better symptom relief, improved cosmetic scores, lower complication rates, shorter duration of hospital stay and reduced operation time[114].

On the basis of the accumulated evidence supporting the use of these procedures, several consensus statements have been issued by international scientific societies regulating their appropriate use and describing the profile of nodules that can benefit from these treatment modalities[115–118]. According to these recommendations, the use of these techniques should be limited to benign lesions causing local pressure or cosmetic concerns, which are typically single or well-defined dominant nodules ≥30 mm with confirmed growth on ultrasonography follow-up[117]. When faced with patients who have large goitres, toxic multinodular goitres or multiple thyroid nodules that cause symptoms, surgery is still the preferred choice[119].

Nodules suspicious for malignancy

This section pertains to nodules with indeterminate cytology (Bethesda class III and IV) that have a suspicious sonography pattern or positive

or high-risk molecular test, or to nodules with Bethesda class V or VI cytology. Not all these nodules warrant surgical removal: active surveillance might be considered as an alternative to immediate surgery for well-selected patients with low-risk cancers. These cases include PTC of less than 10–15 mm in size, with no suspicion of extrathyroidal extension, no evidence of metastatic spread and no worrisome cytological features associated with tumour aggressiveness[8].

Active surveillance. The results of the first active surveillance study at Kuma Hospital in Japan, published in 2003 showed that more than 70% of microPTCs (up to 10 mm) were stable during the observation period, with a negligible risk (~4% in 10 years) of spreading to the locoregional lymph nodes[120]. Furthermore, patients who showed progression or growth of the malignancy and later underwent surgery did not experience increased morbidity or mortality compared with those whose tumours were stable. Similar results were obtained by several subsequent studies, and the option of active surveillance is now supported by several practice guidelines[2,39,121]. A non-randomized controlled trial demonstrated that a similar approach is viable for low-risk PTCs of up to 20 mm (ref. 122).

Active surveillance involves regular neck ultrasound assessments every 6 months until stability is confirmed (2 years of no evidence of progression). The frequency of neck ultrasound assessments is then reduced to every 1–2 years. Surgery is only recommended if the PTC progresses: for example, if it grows in size (by >3 mm) or if suspicious lymph nodes appear. Active surveillance might be a particularly appropriate option for older patients, who have a lower rate of disease progression. The same cases can also be treated with thermal ablative technologies, as outlined above[123]. Surgery and thermal ablation have been demonstrated to have similar outcomes at 5-year follow-up, although thermal ablative technologies resulted in a lower rate of complications and better quality of life than surgery[124,125]. While evidence for the clinical usefulness of thermal ablation accumulates, this treatment is still not the standard of care for low-risk thyroid cancers, which are usually subject to either surveillance or surgery.

Conversely, active surveillance or non-surgical treatments (such as thermal ablation) are not appropriate for patients with tumours with high-risk features (for example, clinical metastasis at diagnosis, signs or symptoms of invasion to the recurrent laryngeal nerve or trachea, and high-grade malignancy on cytology) or for those with tumours involving critical anatomic fields (near to the trachea or located in the pathway of the recurrent laryngeal nerve)[126]. Surgery is suggested in these cases.

Surgery. If surgery is indicated, the minimum extent is lobectomy with isthmusectomy or, rarely, an isthmusectomy alone. A conservative surgical approach offers several advantages over total thyroidectomy[2,127,128]. First, it might obviate the need for lifelong levothyroxine replacement therapy in about half of patients, as the remaining thyroid can synthesize a sufficient amount of thyroid hormone. Furthermore, the rate of surgical complication is lower than that for total thyroidectomy: it virtually eliminates the risks of permanent hypoparathyroidism and bilateral recurrent laryngeal nerve palsy.

For patients with nodules of 1–4 cm, either lobectomy or total thyroidectomy is acceptable. However, for those with larger nodules or with suspicion of extrathyroidal extension or metastases (locoregional or distant), total thyroidectomy is the preferred approach[119]. For patients with indeterminate nodules and positive molecular tests, lobectomy with isthmusectomy is generally advocated. However, thyroidectomy might be necessary for patients with larger indeterminate nodules (≥3–4 cm), progressive enlargement, worrisome sonography features, high-risk molecular alterations, radiation exposure or a family history of thyroid cancer. Further therapeutic options for locally invasive or advanced thyroid cancers are beyond the scope of this review but are thoroughly reviewed elsewhere[105,129].

Patient preference and decision-making tools

Given the variety of clinical scenarios and options available, patients sometimes seek a second medical opinion to reassure themselves of the correct choice of treatment. A retrospective study found that ~35% of the recommendations made by the initial treating physicians did not fully concur with the second medical opinion[130]. The preferences of patients and doctors for treating thyroid nodules and the willingness of these different groups of people to accept certain risks can vary[131,132]. For these reasons, some shared decision-making tools have been developed to improve clinician–patient interactions and discussions about diagnostic and treatment options for thyroid nodules[133]. These tools might improve awareness of diagnostic and therapeutic choices and make it easier for patients to express a preference, which is useful for both patients[134] and clinicians[135].

Conclusions

Most thyroid nodules are benign or presumed benign. A personalized, risk-based protocol that promotes high-quality care and minimizes costs and unnecessary testing and treatment can be achieved by using a diagnostic approach that includes ultrasonography and, when indicated, FNA biopsy and molecular testing. Several challenges remain in sonography risk assessment. Interobserver variability limits consistency but artificial intelligence-powered tools hold promise for improvement. Additionally, broader access to molecular testing is needed in many regions of the world. Finally, wider adoption of active surveillance and minimally invasive approaches would benefit from more robust evidence demonstrating their long-term advantages.

Published online: 16 August 2024

References

1. Borson-Chazot, F., Borget, I., Mathonnet, M. & Leenhardt, L. SFE-AFCE-SFMN 2022 consensus on the management of thyroid nodules: epidemiology and challenges in the management of thyroid nodules. *Ann. Endocrinol.* **83**, 378–379 (2022).
2. Durante, C. et al. 2023 European Thyroid Association clinical practice guidelines for thyroid nodule management. *Eur. Thyroid J.* **12**, e230067 (2023).
These guidelines highlight the need for cost-effective, patient-centred approaches; it is notable that the majority of lesions are benign and asymptomatic and therefore do not necessitate treatment.
3. Uppal, N., Collins, R. & James, B. Thyroid nodules: global, economic, and personal burdens. *Front. Endocrinol.* **14**, 1113977 (2023).
4. Grani, G., Sponziello, M., Pecce, V., Ramundo, V. & Durante, C. Contemporary thyroid nodule evaluation and management. *J. Clin. Endocrinol. Metab.* **105**, 2869–2883 (2020).
5. Li, M., Dal Maso, L. & Vaccarella, S. Global trends in thyroid cancer incidence and the impact of overdiagnosis. *Lancet Diabetes Endocrinol.* **8**, 468–470 (2020).
6. Vaccarella, S. et al. Worldwide thyroid-cancer epidemic? The increasing impact of overdiagnosis. *N. Engl. J. Med.* **375**, 614–617 (2016).
7. Grani, G. et al. Real-world performance of the american thyroid association risk estimates in predicting 1-year differentiated thyroid cancer outcomes: a prospective multicenter study of 2000 patients. *Thyroid* **31**, 264–271 (2021).
8. Ramundo, V. et al. Low-risk papillary thyroid microcarcinoma: optimal management toward a more conservative approach. *J. Surg. Oncol.* **121**, 958–963 (2020).
9. Uppal, N., Cunningham Nee Lubitz, C. & James, B. The cost and financial burden of thyroid cancer on patients in the US: a review and directions for future research. *JAMA Otolaryngol. Head Neck Surg.* **148**, 568–575 (2022).
10. Dean, D. S. & Gharib, H. Epidemiology of thyroid nodules. *Best Pract. Res. Clin. Endocrinol. Metab.* **22**, 901–911 (2008).
11. Mu, C. et al. Mapping global epidemiology of thyroid nodules among general population: a systematic review and meta-analysis. *Front. Oncol.* **12**, 1029926 (2022).
12. Huang, X. et al. Epidemiological survey of thyroid nodules in 2098 patients for routine physical examination in Fujian, China. *Contrast Media Mol. Imaging* **2022**, 2913405 (2022).

13. Tian, C. et al. Iodine nutrition and the prevalence status of thyroid nodules in the population: a cross-sectional survey in Heilongjiang province, China. *Biol. Trace Elem. Res.* **199**, 3181–3189 (2021).
14. Zhang, C., Gao, X., Han, Y., Teng, W. & Shan, Z. Correlation between thyroid nodules and metabolic syndrome: a systematic review and meta-analysis. *Front. Endocrinol.* **12**, 730279 (2021).
15. Zhang, F. et al. The relationship and gender disparity between thyroid nodules and metabolic syndrome components based on a recent nationwide cross-sectional study and meta-analysis. *Front. Endocrinol.* **12**, 736972 (2021).
16. Xu, L. et al. Prevalence and associated metabolic factors for thyroid nodules: a cross-sectional study in Southwest of China with more than 120 thousand populations. *BMC Endocr. Disord.* **21**, 175 (2021).
17. Yan, Y. et al. Risk factors associated with the prevalence of thyroid nodules in adults in Northeast China: a cross-sectional population-based study. *BMJ Open* **13**, e069390 (2023).
18. Li, Y. et al. Prevalence of thyroid nodules in China: a health examination cohort-based study. *Front. Endocrinol.* **12**, 676144 (2021).
19. Yang, H.-X., Zhong, Y., Lv, W.-H., Zhang, F. & Yu, H. Association of adiposity with thyroid nodules: a cross-sectional study of a healthy population in Beijing, China. *BMC Endocr. Disord.* **19**, 102 (2019).
20. Sajisevi, M. et al. Evaluating the rising incidence of thyroid cancer and thyroid nodule detection modes: a multinational, multi-institutional analysis. *JAMA Otolaryngol. Head Neck Surg.* **148**, 811–818 (2022).
This retrospective analysis of thyroid cancer cases revealed that most patients presented with no thyroid-related symptoms; on average, these cancers were smaller than those of patients who presented with symptoms.
21. Sharbidre, K. G., Lockhart, M. E. & Tessler, F. N. Incidental thyroid nodules on imaging. *Radiol. Clin. North Am.* **59**, 525–533 (2021).
22. Wadsley, J. et al. Consensus statement on the management of incidentally discovered FDG avid thyroid nodules in patients being investigated for other cancers. *Clin. Endocrinol.* https://doi.org/10.1111/cen.14905 (2023).
23. US Preventive Services Task Force; Bibbins-Domingo, K. et al. Screening for thyroid cancer: US preventive services task force recommendation statement. *JAMA* **317**, 1882 (2017).
24. Balshem, H. et al. GRADE guidelines: 3. Rating the quality of evidence. *J. Clin. Epidemiol.* **64**, 401–406 (2011).
25. Yi, K. H. The 2017 United States preventive services task force recommendation for thyroid cancer screening is no longer the gold standard. *Endocrinol. Metab.* **38**, 72–74 (2023).
26. Moon, S., Song, Y. S., Jung, K. Y., Lee, E. K. & Park, Y. J. Lower thyroid cancer mortality in patients detected by screening: a meta-analysis. *Endocrinol. Metab.* **38**, 93–103 (2023).
27. Jung, M. Breast, prostate, and thyroid cancer screening tests and overdiagnosis. *Curr. Probl. Cancer* **41**, 71–79 (2017).
28. Wilson, J. M. G. & Jungner, G. *Principles and Practice of Screening for Disease* https://iris.who.int/bitstream/handle/10665/37650/WHO_PHP_34.pdf?sequence=17&isAllowed=y (WHO, 1968).
29. Lamartina, L., Grani, G., Durante, C., Filetti, S. & Cooper, D. S. Screening for differentiated thyroid cancer in selected populations. *Lancet Diabetes Endocrinol.* **8**, 81–88 (2020).
30. Grani, G. et al. Prevalence of thyroid nodules and thyroid cancer in individuals with a first-degree family history of non-medullary thyroid cancer: a cross-sectional study based on sonographic screening. *Thyroid* **32**, 1392–1401 (2022).
31. Grani, G. et al. Ultrasound screening for thyroid nodules and cancer in individuals with family history of thyroid cancer: a micro-costing approach. *J. Endocrinol. Invest.* **46**, 2327–2330 (2023).
32. Grani, G., Del Gatto, V., Cantisani, V., Mandel, S. J. & Durante, C. A reappraisal of suspicious sonographic features of thyroid nodules: shape is not an independent predictor of malignancy. *J. Clin. Endocrinol. Metab.* **108**, e816–e822 (2023).
33. Ramundo, V. et al. Diagnostic performance of neck ultrasonography in the preoperative evaluation for extrathyroidal extension of suspicious thyroid nodules. *World J. Surg.* **44**, 2669–2674 (2020).
34. Solymosi, T. et al. Considerable interobserver variation calls for unambiguous definitions of thyroid nodule ultrasound characteristics. *Eur. Thyroid J.* **12**, e220134 (2023).
35. Grani, G. et al. Reducing the number of unnecessary thyroid biopsies while improving diagnostic accuracy: toward the 'Right' TIRADS. *J. Clin. Endocrinol. Metab.* **104**, 95–102 (2019).
36. Kim, D. H., Kim, S. W., Basurrah, M. A., Lee, J. & Hwang, S. H. Diagnostic performance of six ultrasound risk stratification systems for thyroid nodules: a systematic review and network meta-analysis. *AJR Am. J. Roentgenol.* **220**, 791–803 (2023).
This network meta-analysis compared the diagnostic performance of various ultrasonography RSSs for thyroid nodules: the ACR TIRADS showed the highest sensitivity and specificity.
37. Gharib, H. et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules — 2016 update appendix. *Endocr. Pract.* **22**, 1–60 (2016).
38. Tessler, F. N. et al. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS committee. *J. Am. Coll. Radiol.* **14**, 587–595 (2017).
39. Haugen, B. R. et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: the American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid* **26**, 1–133 (2016).
40. Russ, G. et al. European Thyroid Association guidelines for ultrasound malignancy risk stratification of thyroid nodules in adults: the EU-TIRADS. *Eur. Thyroid J.* **6**, 225–237 (2017).
41. Shin, J. H. et al. Ultrasonography diagnosis and imaging-based management of thyroid nodules: revised korean society of thyroid radiology consensus statement and recommendations. *Korean J. Radiol.* **17**, 370 (2016).
42. Kwak, J. Y. et al. Thyroid imaging reporting and data system for US features of nodules: a step in establishing better stratification of cancer risk. *Radiology* **260**, 892–899 (2011).
43. Ha, E. J. et al. 2021 Korean thyroid imaging reporting and data system and imaging-based management of thyroid nodules: Korean Society of Thyroid Radiology consensus statement and recommendations. *Korean J. Radiol.* **22**, 2094–2123 (2021).
44. Lee, M. K. et al. Standardized imaging and reporting for thyroid ultrasound: Korean society of thyroid radiology consensus statement and recommendation. *Korean J. Radiol.* **24**, 22–30 (2023).
45. Zhou, J. et al. 2020 Chinese guidelines for ultrasound malignancy risk stratification of thyroid nodules: the C-TIRADS. *Endocrine* **70**, 256–279 (2020).
46. Tumino, D. et al. Nodular thyroid disease in the era of precision medicine. *Front. Endocrinol.* **10**, 907 (2020).
47. Hoang, J. K. et al. An international survey on utilization of five thyroid nodule risk stratification systems: a needs assessment with future implications. *Thyroid* **32**, 675–681 (2022).
48. Grani, G. et al. Taller-than-wide shape: a new definition improves the specificity of TIRADS systems. *Eur. Thyroid J.* **9**, 85–91 (2020).
49. Kim, S. Y., Na, D. G. & Paik, W. Which ultrasound image plane is appropriate for evaluating the taller-than-wide sign in the risk stratification of thyroid nodules? *Eur. Radiol.* **31**, 7605–7613 (2021).
50. Ramundo, V. et al. Is thyroid nodule location associated with malignancy risk? *Ultrasonography* **38**, 231–235 (2019).
51. Jasim, S., Baranski, T. J., Teefey, S. A. & Middleton, W. D. Investigating the effect of thyroid nodule location on the risk of thyroid cancer. *Thyroid* **30**, 401–407 (2020).
52. Tessler, F. N. Thyroid nodules and real estate: location matters. *Thyroid* **30**, 349–350 (2020).
53. Grani, G. et al. Sonographic risk stratification systems for thyroid nodules as rule-out tests in older adults. *Cancers* **12**, 2458 (2020).
54. Perkins, J. M. & Papaleontiou, M. Towards de-implementation of low-value thyroid care in older adults. *Curr. Opin. Endocrinol. Diabetes Obes.* **29**, 483–491 (2022).
55. Cozzolino, A. et al. Diagnostic accuracy of ultrasonographic features in detecting thyroid cancer in the transition age: a meta-analysis. *Eur. Thyroid J.* **11**, e220039 (2022).
56. Walter, L. B. et al. Age-related variation in malignant cytology rates of thyroid nodules: insights from a retrospective observational study assessing the ACR TI-RADS. *Eur. J. Endocrinol.* **189**, 584–589 (2023).
57. Durante, C. et al. International expert consensus on US lexicon for thyroid nodules. *Radiology* **309**, e231481 (2023).
An international, multidisciplinary group of 19 physicians with expertise in thyroid sonography was assembled with the objective of developing a lexicon and atlas that would standardize the terminology used in describing thyroid nodules.
58. Tessler, F. N. & Thomas, J. Artificial intelligence for evaluation of thyroid nodules: a primer. *Thyroid* **33**, 150–158 (2023).
59. Xue, Y. et al. Accuracy of ultrasound diagnosis of thyroid nodules based on artificial intelligence-assisted diagnostic technology: a systematic review and meta-analysis. *Int. J. Endocrinol.* **2022**, 9492056 (2022).
60. Potipimpanon, P., Charakorn, N. & Hirunwiwatkul, P. A comparison of artificial intelligence versus radiologists in the diagnosis of thyroid nodules using ultrasonography: a systematic review and meta-analysis. *Eur. Arch. Otorhinolaryngol.* **279**, 5363–5373 (2022).
61. Ha, E. J. et al. Artificial intelligence model assisting thyroid nodule diagnosis and management: a multicenter diagnostic study. *J. Clin. Endocrinol. Metab.* **109**, 527–535 (2024).
Describes a deep learning-based artificial intelligence model with the potential to enhance diagnostic performance and interobserver agreement in the diagnosis of thyroid cancer.
62. Fresilli, D. et al. Computer-aided diagnostic system for thyroid nodule sonographic evaluation outperforms the specificity of less experienced examiners. *J. Ultrasound* **23**, 169–174 (2020).
63. Giovanella, L. et al. EANM practice guideline/SNMMI procedure standard for RAIU and thyroid scintigraphy. *Eur. J. Nucl. Med. Mol. Imaging* **46**, 2514–2525 (2019).
64. Musholt, T. J. et al. German Association of Endocrine Surgeons practice guidelines for the surgical treatment of benign thyroid disease. *Langenbecks Arch. Surg.* **396**, 639–649 (2011).
65. Giovanella, L., Ceriani, L. & Treglia, G. Role of isotope scan, including positron emission tomography/computed tomography, in nodular goitre. *Best Pract. Res. Clin. Endocrinol. Metab.* **28**, 507–518 (2014).
66. Trimboli, P., Mian, C., Piccardo, A. & Treglia, G. Diagnostic tests for medullary thyroid carcinoma: an umbrella review. *Endocrine* **81**, 183–193 (2023).
67. Elisei, R. et al. Impact of routine measurement of serum calcitonin on the diagnosis and outcome of medullary thyroid cancer: experience in 10,864 patients with nodular thyroid disorders. *J. Clin. Endocrinol. Metab.* **89**, 163–168 (2004).
68. Costante, G., Durante, C., Francis, Z., Schlumberger, M. & Filetti, S. Determination of calcitonin levels in C-cell disease: clinical interest and potential pitfalls. *Nat. Clin. Pract. Endocrinol. Metab.* **5**, 35–44 (2009).
69. Fugazzola, L. et al. Basal and stimulated calcitonin for the diagnosis of medullary thyroid cancer: updated thresholds and safety assessment. *J. Endocrinol. Invest.* **44**, 587–597 (2021).

70. Trimboli, P. et al. Detection rate of FNA cytology in medullary thyroid carcinoma: a meta-analysis. *Clin. Endocrinol.* **82**, 280–285 (2015).
71. Ali, S. Z. et al. The 2023 Bethesda system for reporting thyroid cytopathology. *J. Am. Soc. Cytopathol.* **12**, 319–325 (2023).
This study presents an overview of the novel features incorporated into the third edition of the BSRTC, a standardized, category-based reporting system for thyroid FNAs.
72. Pradeep, I., Joshi, A., Rath, A., Bharti, J. N. & Nigam, J. S. Overview of updates in new The Bethesda System for Reporting of Thyroid Cytopathology using the latest WHO thyroid tumor classification terminology. *Endocr. Pract.* **29**, 1020–1022 (2023).
73. Nardi, F. et al. Italian consensus for the classification and reporting of thyroid cytology. *J. Endocrinol. Invest.* **37**, 593–599 (2014).
74. Hirokawa, M. et al. The Japanese reporting system for thyroid aspiration cytology 2019 (JRSTAC2019). *Gland. Surg.* **9**, 1653–1662 (2020).
75. The Royal College of Pathologists of Australasia. *Thyroid Cytology Structured Reporting Protocol* 2nd Ed (RCPA, 2019).
76. The Royal College of Pathologists. *Guidance on the Reporting of Thyroid Cytology Specimens* https://bahno.org.uk/_userfiles/pages/files/g089_guidance_on_the_reporting_of_thyroid_cytology_for_publication.pdf (2022).
77. Poller, D. N., Bongiovanni, M. & Trimboli, P. Risk of malignancy in the various categories of the UK Royal College of Pathologists Thy terminology for thyroid FNA cytology: a systematic review and meta-analysis. *Cancer Cytopathol.* **128**, 36–42 (2020).
78. Stewart, R. et al. Quantifying the differences in surgical management of patients with definitive and indeterminate thyroid nodule cytology. *Eur. J. Surg. Oncol.* **46**, 252–257 (2020).
79. Grani, G., Sponziello, M., Filetti, S. & Durante, C. Molecular analysis of fine-needle aspiration cytology in thyroid disease: where are we? *Curr. Opin. Otolaryngol. Head Neck Surg.* **29**, 107–112 (2021).
80. Patel, J., Klopper, J. & Cottrill, E. E. Molecular diagnostics in the evaluation of thyroid nodules: current use and prospective opportunities. *Front. Endocrinol.* **14**, 1101410 (2023).
81. Grani, G. et al. Ultrasonography scoring systems can rule out malignancy in cytologically indeterminate thyroid nodules. *Endocrine* **57**, 256–261 (2017).
82. Qiu, Y. et al. Diagnostic reliability of elastography in thyroid nodules reported as indeterminate at prior fine-needle aspiration cytology (FNAC): a systematic review and Bayesian meta-analysis. *Eur. Radiol.* **30**, 6624–6634 (2020).
83. Cantisani, V. et al. US-elastography with different techniques for thyroid nodule characterization: systematic review and meta-analysis. *Front. Oncol.* **12**, 845549 (2022).
84. Trimboli, P. et al. Performance of contrast-enhanced ultrasound (CEUS) in assessing thyroid nodules: a systematic review and meta-analysis using histological standard of reference. *Radiol. Med.* **125**, 406–415 (2020).
85. Nikiforova, M. N. et al. Analytical performance of the ThyroSeq v3 genomic classifier for cancer diagnosis in thyroid nodules. *Cancer* **124**, 1682–1690 (2018).
86. Steward, D. L. et al. Performance of a multigene genomic classifier in thyroid nodules with indeterminate cytology: a prospective blinded multicenter study. *JAMA Oncol.* **5**, 204 (2019).
87. Vuong, H. G., Nguyen, T. P. X., Hassell, L. A. & Jung, C. K. Diagnostic performances of the afirma gene sequencing classifier in comparison with the gene expression classifier: a meta-analysis. *Cancer Cytopathol.* **129**, 182–189 (2021).
88. Patel, K. N. et al. Performance of a genomic sequencing classifier for the preoperative diagnosis of cytologically indeterminate thyroid nodules. *JAMA Surg.* **153**, 817–824 (2018).
89. Hu, M. I. et al. Afirma genomic sequencing classifier and xpression atlas molecular findings in consecutive Bethesda III-VI thyroid nodules. *J. Clin. Endocrinol. Metab.* **106**, 2198–2207 (2021).
90. Munoz-Zuluaga, C. A. et al. Use of the Afirma Xpression Atlas for cytologically indeterminate, Afirma Genomic Sequencing Classifier suspicious thyroid nodules: clinicopathologic analysis with postoperative molecular testing. *Am. J. Clin. Pathol.* **161**, 463–468 (2024).
91. Livhits, M. J. et al. Effectiveness of molecular testing techniques for diagnosis of indeterminate thyroid nodules: a randomized clinical trial. *JAMA Oncol.* **7**, 70–77 (2021).
92. Ohori, N. P. et al. Benign call rate and molecular test result distribution of ThyroSeq v3. *Cancer Cytopathol.* **127**, 161–168 (2019).
93. Dharampal, N. et al. Cost-effectiveness analysis of molecular testing for cytologically indeterminate thyroid nodules. *J. Otolaryngol. Head Neck Surg.* **51**, 46 (2022).
94. Nicholson, K. J., Roberts, M. S., McCoy, K. L., Carty, S. E. & Yip, L. Molecular testing versus diagnostic lobectomy in Bethesda III/IV thyroid nodules: a cost-effectiveness analysis. *Thyroid* **29**, 1237–1243 (2019).
95. Ontario Health (Quality). Molecular testing for thyroid nodules of indeterminate cytology: a health technology assessment. *Ont. Health Technol. Assess. Ser.* **22**, 1–111 (2022).
96. Huang, Y. et al. Does the adoption of molecular testing cause decreased thyroidectomy rates in a national cohort? A quasiexperimental study of high- versus low-adoption states. *Thyroid* **34**, 388–398 (2024).
97. Paschke, R. Why did the rapid increase of reflex molecular testing of indeterminate fine needle aspiration cytologies in the USA not impact thyroidectomy rates? What is the lesson to be learned? *Thyroid* **34**, 290–291 (2024).
98. Hu, T. X. et al. The effect modification of ultrasound risk classification on molecular testing in predicting the risk of malignancy in cytologically indeterminate thyroid nodules. *Thyroid* **32**, 905–916 (2022).
99. Stewardson, P. et al. Prospective validation of ThyroSPEC molecular testing of indeterminate thyroid nodule cytology following diagnostic pathway optimization. *Thyroid* **33**, 1423–1433 (2023).
100. Paschke, R. et al. European Thyroid Association guidelines regarding thyroid nodule molecular fine-needle aspiration cytology diagnostics. *Eur. Thyroid J.* **6**, 115–129 (2017).
101. Hall, E. A., Hartzband, P., VanderLaan, P. A. & Nishino, M. Risk stratification of cytologically indeterminate thyroid nodules with nondiagnostic or benign cytology on repeat FNA: implications for molecular testing and surveillance. *Cancer Cytopathol.* **131**, 313–324 (2023).
102. Nishino, M. et al. Repeat fine needle aspiration cytology refines the selection of thyroid nodules for Afirma gene expression classifier testing. *Thyroid* **31**, 1253–1263 (2021).
103. Chiosea, S. et al. Molecular profiling of 50,734 Bethesda III-VI thyroid nodules by ThyroSeq v3: implications for personalized management. *J. Clin. Endocrinol. Metab.* **108**, 2999–3008 (2023).
Molecular profiling of Bethesda III–VI thyroid nodules can prevent unnecessary surgical intervention in a significant subset of patients, whilst also providing prognostic and therapeutic information to those who require it.
104. Finkelstein, S. D. et al. A retrospective evaluation of the diagnostic performance of an interdependent pairwise MicroRNA expression analysis with a mutation panel in indeterminate thyroid nodules. *Thyroid* **32**, 1362–1371 (2022).
105. Boucai, L., Zafereo, M. & Cabanillas, M. E. Thyroid cancer: a review. *JAMA* **331**, 425 (2024).
106. Leboulleux, S. et al. SFE-AFCE-SFMN 2022 Consensus on the management of thyroid nodules: follow-up: how and how long? *Ann. Endocrinol.* **83**, 407–414 (2022).
107. Grussendorf, M., Ruschenburg, I. & Brabant, G. Malignancy rates in thyroid nodules: a long-term cohort study of 17,592 patients. *Eur. Thyroid J.* **11**, e220027 (2022).
108. Durante, C. et al. The natural history of benign thyroid nodules. *JAMA* **313**, 926–935 (2015).
A prospective, multicentre, observational study examining the frequency, magnitude and factors associated with changes in the size of benign thyroid nodules.
109. Xiang, P. et al. Identifying and predicting diverse patterns of benign nodule growth. *J. Clin. Endocrinol. Metab.* **108**, e458–e463 (2023).
110. Grani, G. et al. Sonographically estimated risks of malignancy for thyroid nodules computed with five standard classification systems: changes over time and their relation to malignancy. *Thyroid* **28**, 1190–1197 (2018).
111. Chou, R. et al. Ultrasound follow-up of benign thyroid nodules: a scoping review. *Thyroid* **33**, 420–427 (2023).
112. Bonnema, S. J. & Hegedüs, L. Radioiodine therapy in benign thyroid diseases: effects, side effects, and factors affecting therapeutic outcome. *Endocr. Rev.* **33**, 920–980 (2012).
113. Benaim, E. H. et al. High-intensity focused ultrasound for benign thyroid nodules: systemic review and meta-analysis. *Am. J. Otolaryngol.* **44**, 103999 (2023).
This study assesses the effectiveness and safety of high-intensity focused ultrasound in the treatment of benign thyroid nodules.
114. Ding, J., Wang, D., Zhang, W., Xu, D. & Wang, W. Ultrasound-guided radiofrequency and microwave ablation for the management of patients with benign thyroid nodules: systematic review and meta-analysis. *Ultrasound Q.* **39**, 61–68 (2023).
115. Jasim, S. et al. American Association of Clinical Endocrinology Disease state clinical review: the clinical utility of minimally invasive interventional procedures in the management of benign and malignant thyroid lesions. *Endocr. Pract.* **28**, 433–448 (2022).
Minimally invasive techniques for the management of benign and malignant thyroid lesions have proven effective and safe in the hands of experienced medical practitioners.
116. Sinclair, C. F. et al. General principles for the safe performance, training, and adoption of ablation techniques for benign thyroid nodules: an American Thyroid Association Statement. *Thyroid* **33**, 1150–1170 (2023).
This statement emphasizes the importance of adopting standardized protocols for ablation procedures to ensure consistency and quality across different healthcare settings.
117. Papini, E., Monpeyssen, H., Frasoldati, A. & Hegedüs, L. 2020 European Thyroid Association Clinical Practice Guideline for the Use of Image-Guided Ablation in Benign Thyroid Nodules. *Eur. Thyroid J.* **9**, 172–185 (2020).
118. Orloff, L. A. et al. Radiofrequency ablation and related ultrasound-guided ablation technologies for treatment of benign and malignant thyroid disease: an international multidisciplinary consensus statement of the American Head and Neck Society Endocrine Surgery Section with the Asia Pacific Society of Thyroid Surgery, Associazione Medici Endocrinologi, British Association of Endocrine and Thyroid Surgeons, European Thyroid Association, Italian Society of Endocrine Surgery Units, Korean Society of Thyroid Radiology, Latin American Thyroid Society, and Thyroid Nodules Therapies Association. *Head Neck* **44**, 633–660 (2022).
This consensus statement aims to provide a comprehensive and evidence-based guide for the use of radiofrequency ablation and related ultrasound-guided ablation technologies in the treatment of benign and malignant thyroid disease.
119. Patel, K. N. et al. The American Association of Endocrine Surgeons guidelines for the definitive surgical management of thyroid disease in adults. *Ann. Surg.* **271**, e21–e93 (2020).
120. Ito, Y. et al. An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid* **13**, 381–387 (2003).

121. Filetti, S. et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann. Oncol.* **30**, 1856–1883 (2019).
122. Ho, A. S. et al. Expanded parameters in active surveillance for low-risk papillary thyroid carcinoma: a nonrandomized controlled trial. *JAMA Oncol.* **8**, 1588–1596 (2022).
123. Mauri, G. et al. European Thyroid Association and Cardiovascular and Interventional Radiological Society of Europe 2021 clinical practice guideline for the use of minimally invasive treatments in malignant thyroid lesions. *Eur. Thyroid J.* **10**, 185–197 (2021).
124. Yan, L., Zhang, M., Song, Q. & Luo, Y. Ultrasound-guided radiofrequency ablation versus thyroid lobectomy for low-risk papillary thyroid microcarcinoma: a propensity-matched cohort study of 884 patients. *Thyroid* **31**, 1662–1672 (2021).
125. Li, X. et al. Long-term outcomes and risk factors of radiofrequency ablation for t1n0m0 papillary thyroid carcinoma. *JAMA Surg.* **159**, 51–58 (2024).
126. Brito, J. P., Ito, Y., Miyauchi, A. & Tuttle, R. M. A clinical framework to facilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma. *Thyroid* **26**, 144–149 (2016).
127. Park, J. H. & Yoon, J. H. Lobectomy in patients with differentiated thyroid cancer: indications and follow-up. *Endocr. Relat. Cancer* **26**, R381–R393 (2019).
128. Matsuzu, K. et al. Thyroid lobectomy for papillary thyroid cancer: long-term follow-up study of 1,088 cases. *World J. Surg.* **38**, 68–79 (2014).
129. Filetti, S. et al. ESMO Clinical Practice Guideline update on the use of systemic therapy in advanced thyroid cancer. *Ann. Oncol.* **33**, 674–684 (2022).
130. Benaim, E., Dudley, S., Grande, P. & Gillespie, M. B. The value of second opinions on thyroid nodule management provided via direct-to-consumer telemedicine service. *Am. J. Otolaryngol.* **44**, 103732 (2023).
131. van Kinschot, C. M. J. et al. Preferences of patients, clinicians, and healthy controls for the management of a Bethesda III thyroid nodule. *Head Neck* **45**, 1772–1781 (2023). **The findings of a cross-sectional survey indicate that the real-life risks associated with active surveillance and hemithyroidectomy are either equivalent to or lower than those that individuals are willing to accept.**
132. Sawka, A. M. et al. Gender differences in fears related to low-risk papillary thyroid cancer and its treatment. *JAMA Otolaryngol. Head Neck Surg.* **149**, 803–810 (2023).
133. Singh Ospina, N. M. et al. Development and pilot testing of a conversation aid to support the evaluation of patients with thyroid nodules. *Clin. Endocrinol.* **96**, 627–636 (2022).
134. Patel Chavez, C. P. et al. Patient feedback receiving care using a shared decision making tool for thyroid nodule evaluation-an observational study. *Endocrine* **80**, 124–133 (2023).
135. Singh Ospina, N. et al. Clinician feedback using a shared decision-making tool for the evaluation of patients with thyroid nodules-an observational study. *Endocrine* **83**, 449–458 (2024).

Acknowledgements
The authors acknowledge the support of the Italian Ministry of Health (Ricerca Finalizzata 2019, Grant no. RF-2019-12370266 to C.D.) and Sapienza University of Rome (Grant no. RG120172B75D0EEA to C.D.).

Author contributions
C.D. and G.G. researched data for the article, contributed substantially to discussion of the content, wrote the article, and reviewed and/or edited the manuscript before submission. M.S. researched data for the article and wrote the article. S.F. contributed substantially to discussion of the content and reviewed and/or edited the manuscript before submission.

Competing interests
The authors declare no competing interests.

Additional information
Peer review information *Nature Reviews Endocrinology* thanks Gilles Russ and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Springer Nature or its licensor (e.g. a society or other partner) holds exclusive rights to this article under a publishing agreement with the author(s) or other rightsholder(s); author self-archiving of the accepted manuscript version of this article is solely governed by the terms of such publishing agreement and applicable law.

© Springer Nature Limited 2024